

Inverse Problems in Ion Channels, Proteins, and Molecular Biology

Ion channels are proteins with a hole down their middle that allow the movement of ions across the otherwise impermeable cell membrane and thereby control an enormous range of biological function, from signalling in the nervous system, to coordination of contraction, particularly in the heart, to transport in most cells and organelles.

The current through an (already) open channel determines important biological properties of channels, cells, and tissues. The amount and type of ionic flux (e.g., carried by Na^+ , K^+ , Ca^{++} and/or Cl^- ions) can now be understood by *existing* physics, chemistry, and mathematics, with little concession to the special complexity often said to characterize biological systems, using a combination of Poisson's equation, Fick's law, and the theory of crowded solutions.

The charge distribution of this theory is the spatial distribution of the charge of the amino acids of the channel protein, which in turn is determined by the sequence of bases in the DNA which is the blueprint (i.e., gene) that codes the protein. *Determining the spatial distribution of charge is a well posed inverse problem of great biological importance amenable to analysis by existing methods of the theory of inverse problem.* 'Reverse engineering' of the channel protein is made much easier by the powerful experimental techniques of molecular biology and genetics that allow specific changes ('mutations') to be made routinely, if not easily, to the channel protein. The reverse engineering is made much easier by the already existing (enormous) experimental literature reporting the current flowing through a single channel molecule, over a range of voltages and concentrations of different types of ions. *The theory of inverse problems can provide important guidance to the design of mutations and choice of solutions and voltages in future experiments.*

The difficulty of determining the properties of the ion channels depends sensitively on what experiments are actually done. Indeed, in the case of the open ionic channel, it is clear that the apparent difficulty and complexity of this biological system comes more from lack of the important experimental information, not from the system itself.

The open ionic channel is much simpler than many of the devices commonly used in our technology. The essential physics can be stated in a few sentences and is as simple as one would expect in a condensed phase that functions at room temperature and atmospheric pressure. Current flow is determined by the nonlinear interaction of migration, diffusion, and crowded charge. Complexity arises from the nonlinear interactions and our ignorance of the parameters of the protein and ions.

It is possible that a significant fraction of the complexity of protein behaviour arises from a similar combination of nonlinearity and lack of knowledge. In that case, the theory of inverse problem would be of central importance to the design and interpretation of experiments done by thousands of molecular biologists every day.